REMARKS

As a preliminary matter, the Applicants have submitted herein a "Supplemental Information Disclosure Statement and Statement of Relatedness" accompanied by the references cited in the disclosure. This information is submitted in satisfaction of the duty of disclosure under 37 C.F.R. §1.56.

In the application, claims 1-14 are pending. A declaration under 37 C.F.R. §1.132 is provided in relation to the arguments set forth below. In addition, an appendix of pending claims is attached for the Examiner's convenience. Favorable consideration of the following comments as they may apply to the outstanding rejections is requested for the reasons that follow.

Rejections Under 35 U.S.C. §103(a)

Claims 1-14 stand rejected under 35 U.S.C. §103(a) as being rendered obvious by Barany, *et al.* (U.S. Patent No. 6,027,889) (hereinafter "Barany") in view of Walt, *et al.* (U.S. Patent No. 6,023,540) (hereinafter "Walt"). Applicants respectfully traverse.

Barany teaches a method of detecting a target nucleic acid sequence involving attaching an adapter nucleic acid sequence to an oligonucleotide ligation assay probe, to form a ligated product. Barany discloses use of an addressable array - an ordered array - to detect the ligated product. As illustrated in Figure 14, the addressable array is, in part, a substrate with different capture probes immobilized at identifiable, fixed locations, *i.e.*, addressable sites (see for example, column 27, lines 10- 15). The presence of a hybridization signal at a known location on the substrate allows determination of the identity of the target sequence. As acknowledged by the Examiner, Barany does not describe using a population of microspheres as a component of the array.

Walt teaches a method for detecting nucleic acid sequences using a substrate with a patterned surface comprising discrete sites (*e.g.*, wells) and a population of microspheres with capture probes. The microspheres are distributed randomly amongst the discrete sites. Since the population of microspheres may contain different capture probes, Walt teaches that

> mixing microspheres with different functionalities results in loss of information regarding the selectivity for each of the corresponding target sequences. . . . There is no way, however, to determine which probe sequence [ ] is generating the activity since the information concerning which microsphere contained which probe sequence was lost when the subpopulations were mixed.

(column 10, lines 50-53). To overcome this problem, each microsphere in the subpopulation is encoded with a common identifying marker, which in one embodiment is a common optical signature (*e.g.*, ratio of two reporter dyes):

> [i]n the present invention, each microsphere in each subpopulation is encoded with a common optical signature. In the illustrated example, the subpoplation represented by microsphere ***10a*** has a two reporter dye ratio of 10:1; the subpopulation of microspheres ***10b*** has a ratio of 1:1 of the same reporter dyes, and subpopulation of microspheres ***10c*** has a ratio 1:10 of the reporter dyes.

(column 10, lines 61-67). In this way, Walt explains

> the randomly mixed subpopulations of microspheres are useful as an analytic chemistry system based on each of the chemical functionalities separately. . . . By identifying the chemical functionalities of the microspheres in which the optical signature has changed, *using the encoded dye combinations, information regarding the chemical identity and concentration of the analyte may be gained* based upon interaction or noninteraction of each functionality contained in the probe.

(column 11, lines 1-14) (emphasis added). Hence, although both Barany and Walt use immobilized capture sequences situated in an array, there is a significant difference in the way Barany and Walt determine the identity of a target sequence hybridized to the capture sequence. Ascertaining the identity of a target sequence in Barany depends on knowing *a*

priori the spatial position of the hybridization signal on the array substrate. In contrast, the identity of a target sequence in Walt is determined during analysis based on the identifying code imparted on individual microspheres. When examined as a whole, the principle operations of Barany and Walt rely on fundamentally different methods of determining the identity of the target nucleic acid hybridized to the array.

When rejecting claims under 35 U.S.C. §103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. See In re Bell, 25 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. §2142. To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also M.P.E.P. §2143. If any one of these criteria is not met, *prima facie* obviousness is not established.

As the Examiner is well aware, the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. See M.P.E.P. § 2143.01. When a obviousness determination depends on a combination of prior art references, there must be a showing of some "teaching, suggestion, or reason" to combine the references. See Gambro Lundia AB v. Baxter Healthcare Corp., 42 USPQ2d 1378 (Fed. Cir. 1997). The "suggestion, teaching or motivation to combine the prior art references may flow from the references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the

problem to be solved." See In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Although a reference need not expressly teach that the disclosure contained in one reference should be combined with one another, "the showing of combinability, in whatever form must nevertheless be clear and particular." See id. at 1617.

Moreover, "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." See M.P.E.P. §2143.01. Neither can the proposed modification change the principle of operation of the reference: a combination requiring a substantial reconstruction and redesign of the elements shown in the primary references as well as a change in the basic principle under which the primary reference construction was designed to operate renders the teaching insufficient for establishing obviousness. See id.

The Examiner contends that "it would have been obvious to modify the array of Barany, *et al.* to further comprise microspheres wherein the microspheres are distributed on the array" to detect target sequences. However, the Applicants submit that there is no teaching, suggestion or motivation to combine Barany with Walt to arrive at the claimed methods. As the Examiner has concluded, Barany does not teach or suggest an array comprising a population of microspheres. Walt does not teach or suggest attaching a first adapter nucleic acid to a first target nucleic acid sequence to form a modified first target nucleic acid sequence, and hybridizing the modified target sequence to a capture probe on a microsphere. Consequently, there is no teaching or suggestion to combine the array of Barany with the microspheres of Walt.

Moreover, modifying the array of Barany by adapting the microspheres of Walt changes the principle operation of Barany. In Barany, the *ordered* array uses the predetermined information of spatial location of the capture probe on the substrate to

determine the type of target sequence hybridized to the capture probe. In Walt, the information encoded onto each microsphere allows determining the target sequence during analysis, and therefore does not require a spatially fixed, addressable location. Modifying Barany with the method of Walt would render the ordered, addressable array described in Barany superfluous since the microspheres contain their own encoding information. In essence, the asserted combination changes the essential concept of the addressable array of Barany. Thus, although the Examiner is correct in describing generally that both Barany and Walt uses capture sequences immobilized on substrates to detect target sequences, the Examiner has not considered all that the prior art references teach, especially the features in the prior art that would defeat any motivation to combine the references. See M.P.E.P. §2141.02.

Because Barany and Walt describe different compositions using different bases for identifying the target sequences, there is no foundation to conclude that the idea of combining them flows logically from teachings of the references individually. To the contrary, the differences inherent in Barany and Walt logically argue against combining these prior art references.

The Examiner cites several specific reasons for combining Barany with Walt, including an asserted benefit of "individual identification of thousands of captured target sequences" by use of microspheres, the "extremely uniform" signals produced by monodisperse microspheres, and the ability to detect and analyze the signals rapidly using commercially available microscopy instruments and computer software. The Examiner, however, appears to agree that Barany also teaches high density arrays as evidenced from Examiner's statement that "one skilled in the art would have been motivated to modify the high density array of Barany, et al. with the arrayed microspheres of Walt." Moreover, even

if each discrete site in Barany comprised a microsphere, there is no suggested advantage since it would be limited by the number of *addressable sites* that could be fitted onto the substrate. In addition, Barany discloses use of known detection instrumentation (*e.g.*, confocal microscopy) and use of computers to analyze the signals generated by hybridization of target sequences to capture probes (column 36, lines 57-67). Given these facts, the Examiner has not explained the specific understanding or principle of the prior art references that would provide the necessary motivation to modify the array of Barany, but has only provided generalized statements about the characteristics of the compositions described in Walt. That is, the Examiner does not provide specific reasons in the teachings of Walt and Barany, or the knowledge of those skilled in the art, that the arrays of Barany have some disadvantage such that it would benefit from the use of microspheres, or of any advancements or improvements provided by the asserted combination. See Winner Int'l Royalty Corp. v. Wang, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000); see also In re Sernaker, 21 USPQ 1, 5 (Fed. Cir. 1983). Motivation does not concern what is feasible but what is desirable. See Winner Int'l Royalty Corp. at 1587.

Moreover, the Examiner has not defined the nature of the problem confronting the skilled artisan that might provide the motivation to arrive at the proposed solution, namely a combination of Barany and Walt that would supposedly lead to the method of claims 1 and 14. The asserted broad conclusory statements regarding the teachings of the prior art references are not sufficient to show the required motivation. See In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); see also In re Lee, 61 USPQ2d 1430 (Fed. Cir. 2002) ("The need for specificity pervades this authority . . . . [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed," citing In re Kotzab, 55

USPQ2d 1313, 1317 (Fed. Cir. 2000)).

In conclusion, Barany in view of Walt fail to render claims 1 and 14 *prima facie* obvious. As acknowledged by the Examiner, Barany does not disclose the use of microspheres to detect target nucleic acids. Walt does not teach or suggest attaching an adapter nucleic acid to a target nucleic acid to form a modified target nucleic acid. Importantly, the asserted combination renders the ordered, addressable array of Barany irrelevant, and thus fundamentally changes the way Barany operates. As a result, neither Barany nor Walt, taken alone or in combination, provides the necessary teaching, suggestion or motivation to combine the references.

Furthermore, secondary considerations weigh against the asserted conclusion of obviousness. The Supreme Court of the United States has stated that secondary considerations such as "commercial success, long-felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." See Graham v. John Deere Co., 148 USPQ 459 (1966).

Following the guidance in Graham, the Federal Circuit has emphatically and repeatedly held that the objective evidence of nonobviousness must be taken into account always and not just when the decision maker is in doubt: "objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached," See Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986); see also Baush & Lomb, Inc. v. Barnes Hindes, Inc., 230 USPQ 1 (Fed. Cir. 1983); see also Jones v. Hardy, 220 USPQ 1021 (Fed. Cir. 1984).

An important secondary consideration scrutinized by the Federal Circuit is commercial acquiescence or the taking of licenses under the patent or technology. See

Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 24 USPQ2d 1321 (Fed. Cir. 1992); see also In re Serneker, 217 USPQ 1 (Fed. Cir 1983). The Federal Circuit has noted that "such real world considerations provide a colorful picture of the state of the art, what was known in the art, and a solid evidentiary foundation on which to rest a nonobviousness determination." See Minnesota Mining & Mfg. Co., 24 USPQ2d at 1335.

As shown in the accompanying declaration of Dr. John Stuelpnagel submitted pursuant to 37 CFR §1.132, in-house fee for service agreements have been made with various companies for Illumina's BeadArray™ detection technology (see Attachment B) for single nucleotide polymorphism (SNP) genotyping. Importantly, the declaration, as well as the agreements described below (see also Attachment C), establish that the agreements arose out of the recognition and acceptance of Illumina's BeadArray™ detection technology, which is encompassed by the subject matter of claims 1 and 14. Hence, there is a nexus between the commercial agreements and the merits of the claims.

As reported in a news release dated June 29, 2001, Illumina signed a commercial agreement with GlaxoSmithKline to provide single nucleotide polymorphism genotyping services on samples provided by GlaxoSmithKline. Under the terms of the agreement, Illumina will use its BeadArray™ detection technology to "score" or determine the frequency of specified SNPs in the sample set. Applicants point out that GlaxoSmithKline is the world's leading research-based pharmaceutical firm and has a leading position in genomics/genetics and in the use of new drug discovery technologies.

In addition, Illumina signed an agreement with Oxagen, a clinical genomics company which uses databases of family studies to identify new drug targets (newsrelease of March 10, 2002). Oxagen is a recognized world leader in advanced genetic analysis with exclusive access to high quality family collection materials for identifying and validating disease

related genes. In the agreement, Illumina will use its BeadArray™ technology for assays of SNPs provided by Oxagen and generate several million genotype calls from the sample collections. The statement of Oxagen's Chief Executive Officer is germane in regards to the reasons for this commercial agreement:

> Illumina's BeadArray platform will give us the sample throughput and the accuracy we need to extract maximum information from our valuable samples.

Thus, the advantages of high sample throughput and accuracy provided by the BeadArray™ detection technology for SNP genotyping is given as a basis for the commercial agreement rather than other factors such as potential conflicts arising from overlapping technology.

Illumina has also signed commercial agreements with various research institutions to provide SNP genotyping services based on its BeadArray™ detection technology. Illumina signed an agreement with Johns Hopkins Medical University, Institute of Genetic Medicine (news release of January 8, 2002) to provide SNP genotyping services on samples provided by the Institute. The Applicants point out that Johns Hopkins is a world renowned institute at the forefront of research of genetic factors associated with various diseases. In other agreements, Illumina will provide genotyping services for scoring SNPs on samples generated by the Boston University Medical Center (news release of January 28, 2002) and University of California, San Diego, Laboratory of Psychiatric Genomics (news release of April 25, 2002), both of which are also highly respected research institutions.

Applicants point out that all of the described commercial agreements involve companies or research centers consisting of personnel highly skilled in the art who would not make commercial agreements in a fashion contrary to their economic interests. Moreover, that the Applicants have been able to establish such agreements even though the patent has not yet issued is further compelling evidence of the nonobviousness of the claimed methods.

Based on all of the foregoing, the Applicants submit that the Examiner has not established a *prima facie* case of obviousness for claims 1 and 14. There is no teaching, suggestion, or motivation to combine or modify Barany in view of Walt to arrive at the claimed methods. Finally, the commercial agreements under secondary consideration analysis underscores the conclusion that the methods of the present claims are not obvious. Since claims 2-13 ultimately depend from claim 1, these dependent claims are patentable for at least the same reasons. Accordingly, Applicants respectfully request withdrawal of the rejection for claims 1-14 under 35 U.S.C. §103(a).

CONCLUSIONS

Applicants submit that the pending claims of the above referenced application are now in condition for allowance and early notification to that effect is requested. If after review the Examiner feels there are further unresolved issues or determines that prosecution of the application would benefit from a telephone interview, the Examiner is requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: 5/20/2002

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Filed under 37 C.F.R. § 1.34(a)

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